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EXAMINER	
SAUNDERS, DAVID A	

ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
082,051	GYSIN et al
Examiner	**Group Art Unit**
SAUNDERS	1647

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☑ Responsive to communication(s) filed on 3/23/04.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

☑ Claim(s) 1-29 is/are pending in the application.

Of the above claim(s) 5-8, 12-22, 24-28, 28-29 is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☑ Claim(s) 1-4, 9-11, 23, 27 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☑ Claim(s) 1-29 are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received: _____.

Attachment(s)

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☑ Notice of Reference(s) Cited, PTO-892

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Interview Summary, PTO-413

☐ Notice of Informal Patent Application, PTO-152

☐ Other _____

Office Action Summary

Claims 1-29 are pending.

Applicant's election with traverse of Group I (claims 1-4, 23 and 27) in Paper No. filed 3/23/04 is acknowledged. The traversal is on the ground(s) that there is no undue search and examination burden for the examiner to consider all Groups, since all claims depend from independent claims reciting the steps of claim 1. This is not found persuasive because applicant's arguments are not convincing that there would be no undue search and examination burden, except for the case of claims 9-11. Thus claims 1-4, 9-11, 23 and 27 will be presently examined; since both claims 1 and 9 recite common steps. Claim 8 of Group II will not be rejoined with Group I, since it has no steps in common with claim 1.

Regarding applicant's argument that all claims depend from claims that recite the steps of or steps in common with claim 1, this argument is unconvincing with respect to products (e.g. antibodies, cognate antigens) and uses thereof (e.g. body treatments, active molecule screening). Applicant is reminded that the product claims are product by process claims and must be examined as products, not tied to the process. Thus there is a much greater search an examination involved than that of searching for the process of claim 1.

Applicant is also in error when he urges that examiner has made a conclusionary argument that the claimed products could be obtained by the "classical" process of obtaining hybridomas. Applicant has clearly admitted in his own disclosure (page 3, lines 9-14) that Smith et al (1995) obtained an antibody against a conformational antigen by a process different from the instant process. It is thus self-serving for

applicant to argue that there is no evidence that the antibodies (an hence all products related thereto and uses thereof) could have been obtained by other methods. Additionally the examiner notes that the art is crowded, and there is a sufficient burden upon the examiner to examine the method steps recited in claims 1 and 9. Even though the examiner might be able to find some of the products and some of the methods of use thereof disclosed in the numerous references cited below, the examiner does not have the time allotted to consider the numerous product and method of use claims and point out reference teachings related to each of these by col. and line number. Further, to examine the product and use thereof claims, the examiner would need to consider numerous other references--e.g. Smith et al (1995) cited at specification page 3. The examiner finally notes that, even if applicant may eventually amend the process claims to an allowable state, the product claims would not of necessity become patentable. Examination burden would thus be undue.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-4, 9-11, 23 and 27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1, line 6 (actual count) "said immunized mice" lack antecedent basis; at line 7 "the hybridoma" lacks antecedent basis.

In claim 2 "(f)" is confusing since there has been no lettering of steps in claim 1; also, recitation of "optionally" is surplusage; the further limitation(s) recited in any

dependent claim are necessarily optional; at line 2 "the monoclonal antibodies" lack antecedent basis.

In claim 3, the Markush group is improper at line 2 --of--must be inserted after "consisting;" at line 2 recitation of "and" before "cancer antigens" is improper, since "and" is also recited thereafter.

In claim 11, part f) "the monoclonal antibody" lacks antecedent basis; in part g), "the conformational native antigen of interest" lacks antecedent basis; also in part g) "the complex" lacks antecedent basis.

Claim 23 is confusing by reciting "conformational antigen" and "native antigen". What is the relationship of these to the "neo antigen" and "non-self antigen" of claim 1? Since the examiner is unable to determine what this relationship may be, recitations of "conformational" and "native" will not be given any weight in prior art rejections infra.

The term "classical" in claim 23 is a relative term, which renders the claim indefinite. The term " classical" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is not clear which step of base claim 1 is not classical.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 23 and 27 are rejected under 35 U.S.C. 102(b) as being anticipated by Yoshida et al (4,892,934).

Yoshida et al show the preparation of monoclonal antibodies specific for tumor cell antigens (i.e. neo antigens or cancer cell antigens).

Yoshida et al '934 render neonatal mice tolerant to normal tissue, cells, or fragments thereof---e.g. see col.2, line 60-col.3, line 29; col.7, line 61-col.8, line 5.

Yoshida et al then immunize the thus tolerized mice with tumor tissue, cells, or fragments thereof---e.g. see col.3, lines 31-68; col.8, lines 5-27.

The immunized mice are then bled and their sera are each tested for the presence of antibodies to tumor cells and the absence of antibodies to normal cells. This screening process serves to "detect" the immunized animals which are tolerant to the normal cells ---e.g. col. 5 lines 9-20; col. 8, line 52-col.9, line 10; col.9, lines 46-52.

The thus detected animals are used for the preparation of spleen cells, which are fused with myeloma cells, to form hybridomas ---e.g. col.5, line 29-col.6, line 21; col.9, line 45-col.10, line 14.

Yoshida et al '934 then select those growing hybridomas which produce antibody to tumor cell antigens but not to normal cell antigens –e.g. col.6, lines 22-43; col.10, lines 14-23.

Yoshida et al thus show all steps of instant claim 1. Claim 1 does not require that the steps be conducted in order; therefore, the fact that "detecting" of tolerant animals is accomplished after the immunization with tumor cells does not detract from anticipation.

Alternatively, if applicant considers that steps of claim 1 are to be conducted in order, then note that recitation of "detecting said tolerant animal" sets forth no particular process steps. The claim is thus to be read with such breadth that merely identifying the cage that houses the tolerized mice, prior to immunization with the tumor cells, serves to accomplish the "detecting".

Regarding dependent claim 2, note Yoshida et al '934 at col.6, line 44 –col.7, line 24; col. 10, lines 25-50.

Claim 23 is included because, firstly, the examiner cannot determine what is meant by "conformational" or "native" by way of further limiting base claim 23, nor can the examiner determine from applicant's disclosure what particular aspect of applicant's method would assure that the antibodies obtained instantly are directed to "conformational" or "native" antigens while those of the reference would not. Secondly the examiner includes claim 23 because the mere recitation of "200 times greater" adds nothing distinguishable over Yoshida et al. While Yoshida et al do not teach a "200 times greater" yield of hybridomas, they do teach that their method provides for a better yield of hybridomas producing desired antibodies against tumor cells than can be obtained by methods that applicant considers to be "classical" --e.g. col. 1, line 37 – col.2, line 8. since Yoshida et al's method is indistinguishable from applicant's, it is taken that both Yoshida et al and applicant would inherently achieve the capability of yielding "200 times" more hybridomas upon immunization.

Claims 1-3, 9-11, 23 and 27 are rejected under 35 U.S.C. 102(b) as being anticipated by Imam et al (5,851,830).

Imam et al prepare monoclonal antibodies against an antigen present on normal mammary epithelial cells but not on malignant mammary epithelial cell lines.

Imam et al first tolerize neonatal mice by injecting the malignant cell line. They then identify those mice thus treated which are, in fact, tolerant by testing sera from each of the mice for the presence or absence of antibodies against the malignant cell line. Mice lacking such antibodies are then immunized with the normal cell line. The immunized mice are then bled, and sera from each are tested for the absence of antibodies against malignant cells tissue and the presence of antibodies against normal cells/tissue. See col.4, line 48-col.5, line 10, for example. Therein Imam et al show the first three steps of instant claims 1 and 9.

Imam et al further show, the preparation of hybridoma cells by fusing spleen cells from an immunized mouse with myeloma cells. Hybridomas secreting antibodies against normal, but not malignant, cell lines are then selected. See col.5, line 53-col.6, line 12, for example. Imam et al thus show the 4^{th} and 5^{th} steps of instant claims 1 and 9.

From the above, claim 1 is anticipated. While the antibodies of Imam et al are directed against an antigen on normal cells, rather against a "neo-antigen" on tumors/malignant cells, it is to be noted that applicant defines (page 5, lines 12+) the term "neo-antigen" in a broad sense, as reflecting only an antigen present in one but not another differentiation state of a cell. Since malignant and normal cells represent two differentiation states, the examiner properly considers the antigen on the normal epithelial cells of Imam et al as a "neo-antigen."

Regarding claim 2, Imam et al show the purification of monoclonal antibodies at col.7, lines 6-33.

Regarding steps f) and g) of claim 9 and the steps of claim 10, these are anticipated by the SDS-PAGE analysis of immunopreciplates shown at col.6, lines 56-67.

Regarding claims 3 and 11, these are anticipated, since the antigen of Imam et al is present on epithelial cells during a normal stage of development.

Claim 23 is rejected following rational stated supra for Yoshida et al '934.

Claims 1, 3, 23 and 27 are rejected under 35 U.S.C. 102(b) as being anticipated by Matthew et al (Jour Immunol meth, 100, 73, 1987).

Matthew et al prepare monoclonal antibodies specific for postnatal (11 day) rat cerebellum. They first prepare a tissue homoginate of newborn rat cerebellum (this is taken to inherently contain cells or tissue fragments of cells) and then use this preparation to tolerize mice by co-administering cyclophosphamide. They then test sera from each of the thus treated mice for antibodies to new-born rat cerebellum; lack thereof confirms a state of tolerance. The tolerant mice were then immunized with a similar homogenate of postnatal rat cerebellum. Spleen cells were then obtained for fusion to prepare hybridomas. Matthew et al then screen for hybridomas secreting antibodies reactive with postnatal, but not neonatal, rat cerebellum.

Applicant is referred to immunization designated as "DI" at page 74, col.2 and page 77, cols. 1-2. These teachings show all steps of claim 1.

Regarding claim 3, the antigens of the postnatal rat cerebellum but not the neonatal cerebellum are directed against an antigen associated with "normal development."

Regarding claim 23, note Table I (pg.79) shows 85% of the hybridomas of the DI immunization yielded antibodies that distinguish post natal from neonatal antigens of rat cerebellum. Table I also shows 0% of the hybridomas of the DI* immunization (no tolerizing treatment) can thus distinguish post natal from neonatal antigens. A ratio of 85% over 0% is infinite, which is clearly greater than "200 times"; thus claim 23 is anticipated.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 9-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yoshida et al '934 in view of Yoshida et al (5,580,740).

Yoshida et al '934 have been cited supra against claim 1, which has the same steps as a) –e) of claim 9. Yoshida et al '934 were also cited against claims 2-3 since they show how to purify the monoclonal antibodies produced by hybridomas and since the antibodies are specific for neo antigens of cancer cells.

Yoshida et al '740 show that it is conventional to characterize the cognate antigen of an anti-tumor cell antibody by western blotting--e.g. col. 6, lines 48-57; col.14,

lines 26-60; col.15 line 55-col.16, line 6. Steps f) –g) of instant claim 9 and the further step of claim 10 are consistent with the steps conducted in western blotting.

Since it is conventional to thus identify the cognate antigen of a monoclonal antibody specific for tumor cells it would have been obvious to identify the cognate antigen of any monoclonal antibody specific for tumor cells produced by the method of Yoshida et al '934. Further nexus between the two Yoshida et al references is provided by the fact the Yoshida et al '740 point to immunizing animals that are tolerant to normal cells (col.3, lines 34-55).

Claims 1-3, 9-11, 23 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yoshida et al (5,580,740) in view of Yoshida et al ('934).

Yoshida et al '740 teach the preparation of monoclonal antibodies against neo-antigens on adenocarcinoma cells. The protocol set forth at col.3 lines 34-55 follows a method essentially the same as that discussed supra regarding Yoshida et al '934.

The full details of this method of first tolerizing mice against normal cells, then immunizing the mice with tumor/cancer cells, and then selecting the mice having sera with antibodies against tumor cells but not against normal cells has been discussed supra in the 102 rejection over Yoshida et al. Thus to prepare the monoclonal antibody of Yoshida et al '740 it would have been obvious to specifically employ the tolerizing-immunizing method of Yoshida et al '934.

From the above, instant claims 1-3, 23 and 27 would have been obvious. Rejection of claim 27 follows rational set forth for Yoshida et al '934.

Regarding instant claims 9-11, note that steps a)-e) of claim 9 correspond to the steps of claim 1. Yoshida et al show that they characterize the cognate antigen of an anti-tumor cell antibody by western blotting --e.g. col.6, lines 48-57; col.14, lines 26-60; col.15, line 55-col.16, line 6. Steps f) –g) of instant claim 9 and the further step of claim 10 are consistent with the steps conducted in western blotting.

Claims 1-4, 23 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ring (5,849,877) in view of Yoshida et al '934.

Ring teaches the production of monoclonal antibodies against the neo-antigen encoded by the MDR 1 gene. Neonatal mice are first tolerized against 3T3 fibroblasts. They are then immunized with 3T3 fibroblast cells transfected with the MDR 1 gene. Spleen cells from the immunized mice are then fused with myeloma cells to form hybridoma cells. Supernatants of the hybridoma cell cultures are then screening for specific reactivity against the transfected cell line. Ring et al shows all essential aspects of instant claim 1 at col. 14, lines 1-57, except for the step of identifying tolerant animals.

Yoshida et al '934 have been cited further supra for showing a like method of obtaining monoclonal antibodies against neoantigens, by virtue of tolerizing mice with normal cells prior to immunization with cells expressing the neoantigen, as noted supra Yoshida et al show that one should identify those mice which have antibodies reactive with neo-antigen expressing cells, but not with normal cells, by assaying their sera prior to sacrificing and obtaining spleen cells for fusion. Though Ring does not mention such screening, it would have been obvious to have done so with the mice that he had

tolerized and immunized. The motivation to do so would have been to avoid unnecessarily fusing spleen cells from mice that were not showing a specific response to the neo antigen expressing cells. Claim 1 thus would have been obvious.

Regarding claim 2, Ring does not specifically recite purification of the monoclonal antibody from cultured hybridomas; however such would be inherently done, prior to the preparation of antibody fragments (col.8, lines 47-60).

Regarding claim 4, Ring teaches the preparation of humanized antibodies from a murine monoclonal antibody—e.g. col.4, line 41-col.5, line 10; col.9, line 53-col. 10, line 67; col.26, line 62-col.28, line 10.

Regarding claim 23, this is rejected following rational stated supra for Yoshida et al '934.

Claim 27 is rejected since Ring immunizes mice.

Claims 1-3, 23 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yoshida et al '934 in view of either Imam et al and Matthew et al.

Claims 1-3, 9-11, 23 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yoshida et al '740 in view of either Imam et al and Matthew et al.

Both Yoshida et al references have been cited supra against claim 1, with the interpretation that the steps thereof need not be conducted in order--i.e. the "identifying" step is taken as occurring after the "immunizing" step. If claim 1 is interpreted as requiring the steps be conducted in order, then the following rational is applied:

Both Yoshida et al references show a step of tolerization against one set of cellular antigens (e.g. normal cells) and then immunization with a second set of antigens

(e.g. malignant cells), which has numerous antigens in common with the first. Imam et al and Matthew et al teach that, between the tolerizating and immunizing steps, one confirms the tolerant status of the animals.

From these teachings of Matthew et al one would have been motivated to conduct the method of Yoshida et al by confirming the tolerant status of each treated animal prior to immunization. Motivation comes from the fact that Imam et al teach that not all mice administered a tolerizing treatment are, in fact, tolerant (col.4, lines 48+):

Claims 1-4, 9-11, 23 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ring in view of Imam et al and Matthew et al.

Ring has been cited supra for teaching a step of tolerization, followed by a step of immunization. Imam et al and Matthew et al teach identification of the animals that are, in fact, tolerant between these two steps. One would have been motivated to include such an identification step in the method of Ring for reasons set forth in the above paragraph.

Claims 9-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Matthew et al in view of either Imam et al or Yoshida et al '740.

Claims 9-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yoshida et al '934 in view of Imam and Matthew et al as applied to claims 1-3, 23 and 27 are above, and further in view of Imam et al or Yoshida et al '740.

Primary references were cited supra against claim 1, which has same steps as a)-e) of claim 9. The primary references have been noted supra for teaching production of new monoclonal antibodies directed against antigens of a particular stage of cell

differentiation. Imam et al and Yoshida et al '740 both show that, when one obtains a new monoclonal antibody against such antigens, it is conventional to identify the cognate antigen--e.g. by radio-immunoprecipitation or western blotting, the steps of which are encompassed by steps f)-g) of claim 9 and the steps of claim 10. Since Matthew et al and Yoshida et al '934 both obtain new antibodies against such antigens, it would have been obvious to thus identify the cognate antigens thereof.

Claims 1 and 2 are rejected under 35 U.S.C. 103(a) as being unpatentable over Matthew et al in view of any of Yoshida et al ('934 or '740), Imam et al or Ring.

Matthew et al have been cited supra for identifying hybridomas secreting antibodies against antigens present at al particular stage of cell differentiation; they do not explicitly teach purification of the monoclonal antibodies from identified hybridomas. All secondary references show that the further step of purification is conventional and hence obvious.

Claims 1 and 4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yoshida et al '934 in view of Ring.

Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Yoshida et al '740 in view of Yoshida et al '934 as applied to claim 1 above, and further in view of Ring.

Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Yoshida et al '934 in view of Imam et al and Matthew et al as applied to claim 1 above, and further in view of Ring.

Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Yoshida '740 in view of Imam et al and Matthew et al as applied to claim 1 above, and further in view of Ring.

The Yoshida et al '934 and '740 references cited further supra against claim 1 show the preparation of monoclonal antibodies against tumor antigens. Ring also shows preparation of a monoclonal antibody against a tumor cell antigen. He teaches humanization of the antibody for the purpose of reducing host immune responses against the antibody during in vivo use. Yoshida et al teach in vivo use of their antibodies (see '934 at col.7, lines 35+ and '740 at col.1, lines 60-61). It thus would have been obvious to humanize antibodies of Yoshida et al '934 or '740.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Kawai et al (6,258,564) disclose preparation of monoclonal antibodies in mice that have been tolerized by previous injection with like cells at a different stage of differentiation. This reference is taken as cumulative with others cited supra and thus will not be cited in this action.

The information disclosure statement filed 2/6/03 fails to comply with 37 CFR 1.98(a)(1), which requires a list of all patents, publications, or other information submitted for consideration by the Office. It has been placed in the application file, but the information referred to therein has not been considered.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David A. Saunders, PhD whose telephone number is

571-272-0849. The examiner can normally be reached on Monday-Thursday from 8:00a.m to 5:30p.m. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Saunders/tgd

June 7, 2004

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